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(54) METHODS AND COMPOSITIONS FOR IMPROVING APPEARANCE AND FORMATION OF SCAR TISSUE

VERFAHREN UND ZUSAMMENSETZUNGEN ZUR VERBESSERUNG DES AUSSEHENS UND DER BILDUNG VON NARBENGEWEBE

PROCÉDES ET COMPOSITIONS POUR AMÉLIORER L'ASPECT ET LA FORMATION DE TISSU CICATRICIEL

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(56) References cited:
WO-A1-03/051326
WO-A1-2005/105115
WO-A2-2010/131032
US-A- 5 372 807

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Description

FIELD OF THE APPLICATION

[0001] This invention relates to compositions for use in degrading collagen in mammalian skin, thereby improving the appearance and/or reducing the size of a closed wound, which may be a scar or a keloid and cellulite or other conditions wherein excessive collagen is a problem.

BACKGROUND OF THE APPLICATION

[0002] A scar forms in response to cutaneous injury as part of the natural wound healing process. It is a lengthy and continuous process, although it is typically recognized as occurring in stages. The wound healing process begins immediately after injury, with an inflammatory stage. During this stage, which typically lasts from two days to one week (depending on the wound), damaged tissues and foreign matter are removed from the wound. The proliferative stage occurs at a time after the inflammatory stage and is characterized by fibroblast proliferation and collagen and proteoglycan production. It is during the proliferative stage that the extracellular matrix is synthesized in order to provide structural integrity to the wound. The proliferative stage usually lasts about four days to several weeks, depending on the nature of the wound, and it is during this stage when hypertrophic scars usually form. The last stage is called the remodeling stage. During the remodeling stage the previously constructed and randomly organized matrix is remodeled into an organized structure that is highly cross-linked and aligned to increase mechanical strength.

[0003] The changing patterns of the connective tissue matrix during repair following injury require a delicate balance between synthesis and degradation of collagen and proteoglycans. Under normal circumstances this balance is maintained, while in many diseased states, it is altered, leading to an excessive deposition of collagen, to a loss of functional tissue, or to disfigurement. With hypertrophic scars and keloids, the biosynthetic phase continues longer than necessary to repair the wound. In order to maintain nutrient supply, vascular in-growth occurs, resulting in large, highly vascularized scars which are unsightly and can be disabling. Keloids and hypertrophic scars result in functional and cosmetic deformity. They are a common clinical problem.

[0004] While the histological features characterizing hypertrophic scars have been well documented, the underlying pathophysiology is not well known. Hypertrophic scars are a side effect of excessive wound healing, and generally result in the overproduction of cells, collagen, and proteoglycans. Hypertrophic scars are thick and take the form of a raised scar on the skin as a result of overproduction of cells, collagen, and proteoglycans.

[0005] A keloid is a raised scar that exceeds the boundaries of the initial injury (unlike hypertrophic scars which typically stay within the wound boundaries), and is rarely corrected by surgical intervention. Keloids are typically characterized as tumors consisting of highly hyperplastic masses that occur in the dermis and adjacent subcutaneous tissue in susceptible individuals, most commonly following trauma. Keloids may grow into a firm lump that is many times larger than the original scar and are typically fibrotic growths that contain a collection of atypical fibroblasts and an increased abundance of extracellular matrix components, especially collagen.

[0006] Keloids are often more severe than hypertrophic scars, since they tend to invade normal adjacent tissue, while hypertrophic scars tend to remain confined within the original scar border.

[0007] Although commonly benign, hypertrophic scars and keloids often cause discomfort, pain, pruritus, physical disfigurement and impaired quality of life.

Most of the scar reduction products contain silicone in a sheet or gel format, and onion extracts (Mederma Skin Care products). It usually takes over 3 months to see some effect, because these products do not contain effective active ingredient such as any form of collagenase which targets the cause of scar formation. See www.mederma.com/learning/caring_for_scars.

[0008] Such a silicone-based product is described for example in WO 2005/105115 A1.

[0009] Other attempts to treat hypertrophic scars and keloids include surgery, mechanical pressure, steroids, x-ray irradiation and cryotherapy. There are many disadvantages associated with each of these methods. Surgical removal of the scar tissues is often incomplete and can result in further development of hypertrophic scars and keloids at the incision and suture points. Steroid treatments are unpredictable and often result in depigmentation of the skin. X-ray therapy is the only predictable effective treatment to date; however, because of its potential for causing cancer, it is not generally recommended or accepted. The most common approach to controlling scar, and in particular excessive scar formation, is to apply pressure, which appears to be somewhat effective in many instances. This treatment has limited application, generally based on the size and location of the scar tissue on the body. Other commonly used treatments are application of Vitamin E and corticosteroids.

SUMMARY OF THE INVENTION

[0010] This invention relates to a composition comprising a potassium acrylates copolymer having a number average molecular weight of 100,000 or less as measured by gel permeation chromatography calibrated with a poly (methyl methacrylate) standard, for use in a method of improving the appearance of and/or substantially reducing the formation of scars and other visible effects of healed wounds and cellulite, including keloids and hypertrophic scars, comprising, consisting essentially of and consisting of contacting collagen contained within said scar tissue or wound with said composition in an amount effective to degrade said collagen.

[0011] Surprisingly, we have found that low concentrations of certain low molecular weight hydrophobically modified polymers (HmP), more specifically the claimed low molecular weight potassium acrylates copolymers known for their gentle properties are able successfully to degrade collagen located in or around the skin, in particular, in the epithelial layers of the skin. Such polymers also are capable of degrading collagen in extracellular matrix, such as that formed in connection with wound healing and in conjunction with cellulite.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0012] The compositions as described in independent claim 1 can be for use in treating a closed wound having scar tissue on a skin surface of a mammalian subject. Such scar tissue may include a hypertrophic scar and/or a keloid scar.

[0013] Preferably, administering the compositions of this invention may consist essentially of and consist of injecting said compositions into a scar that has formed over a closed wound.

[0014] In another embodiment, it is proposed that the composition may be applied to an open wound prior to scar formation. A composition according to this invention may be applied topically directly to the site of the wound or as part of a bandage, which is placed onto the wound.

[0015] Preferably the compositions of this invention contain at least the potassium acrylates copolymer having a number average molecular weight of 100,000 or less as measured by gel permeation chromatography calibrated with a poly (methyl methacrylate standard and an aqueous solvent. The solvent may be any non-irritating solvent such as deionized water and phosphate buffered saline (PBS), which is acceptable for injection into the scar. In another embodiment, the composition may be a topical composition appropriate for dispensing directly to the surface of the skin, such as a lotion or a cream as described below.

[0016] The compositions of this invention may be deployed to devices that can be applied to skin, including adhesive hydrogel bandages, injectable compositions, kits and methods for ameliorating the formation of scars and/or keloids at a wound site by degrading collagen.

[0017] As used herein, the term "wound" means is a type of injury in which skin is torn, cut or punctured (an *open* wound), or where blunt force trauma causes a contusion (a *closed* wound).

[0018] As used herein, the term "closed wound" may include a hypertrophic scar, keloid, Dupuytren's contracture, fibrotic scar or a reactive scar and the like.

[0019] Preferably, when used in treating scarring of a healed and/or closed wound, the administration of the compositions of this invention comprises, consists essentially of and consists of injecting a composition according to this invention into the scar tissue. Preferably, the composition should be placed below the layer of the stratum corneum, the outmost layer of the skin.

[0020] Preferably, the injectable compositions of this invention contain at least 0.1% of the claimed copolymer and preferably at least 50% solvent including suspensions, colloids, hydrogels, and emulsions, for example, water or water-propylene glycol mixtures. Such compositions may be prepared as injectables, either as liquid solutions or suspensions. Solid forms suitable for dissolving in a hydrogel or a liquid solution, or for suspending in liquid prior to use, can also be prepared. The preparation can also be emulsified. The active ingredient can be mixed with excipients which are pharmaceutically acceptable and compatible with the active ingredient and in amounts suitable for use in the therapeutic methods described herein. Suitable excipients include, for example, water, saline, dextrose, glycerol, ethanol or the like and combinations thereof. In addition, if desired, the composition can contain minor amounts of auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like which enhance the effectiveness of the active ingredient. Details on techniques for formulation and administration may be found in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing Co., Easton, Pa.).

[0021] A composition for use in topical administration preferably contains at least 0.1% of the low molecular weight potassium acrylates copolymer and preferably at least 50% solvent including deionized water and phosphate buffer solution may be incorporated into a bandage or applied directly to the surface of the wound.

[0022] Penetration enhancers/solvents suitable for use in the present invention are alcohols, including, but not limited to, ethanol, propylene glycol, or a combination thereof. Suitable humectants/solvents for use herein, include, but are not limited to, polyethylene glycol, glycerin, sorbitol, xylitol or any combination of any of the foregoing. Suitable anhydrous vehicles for use herein include, but are not limited to, alcohols which may be the same as or different than the alcohol

penetration enhancer. Non-limiting examples of such alcohols are isobutanol and isopropyl alcohol. Mechanical penetration enhancers may also be utilized. Penetration enhancing methods may be found in U.S. Patents Nos. 7,879,823, 7,179,475, 6,890,553 and U.S. Patent Publication No. 2012/0321574.

[0023] As used herein, the term "surfactant" is a surface active agent, or a substance that, when dissolved in water or an aqueous solution, reduces its surface tension or the interfacial tension between it and another liquid.

POLYMERIC MATERIAL

[0024] The polymeric materials used in the compositions of this invention are potassium acrylate copolymers having a number average molecular weight of 100,000 or less as measured by gel permeation chromatography calibrated with a poly(methyl methacrylate) standard.

[0025] As used herein the term "low molecular weight" polymer refers to a polymer having a number average molecular weight (M_n) of 100,000 or less as measured by gel permeation chromatography (GPC) calibrated with a poly(methyl methacrylate) (PMMA) standard. In certain preferred embodiments, low-molecular weight polymers are those having molecular weight ranges of from 5,000 to 80,000 M_n, more preferably from 10,000 to 50,000 M_n, and more preferably between 15,000 and 40,000 M_n.

[0026] Certain hydrophobically-modified polymers and methods of making such polymers are described in U.S. Patent No. 6,433,061, issued to Marchant et al. The polymeric materials useful in the composition of this invention are preferably non-crosslinked, linear acrylic copolymers that are very mild to the skin and mucosa. These non-crosslinked, linear polymers are of low molecular weight having a number average molecular weight of 100,000 or less as measured by gel permeation chromatography (GPC) calibrated with a poly(methyl methacrylate) (PMMA) standard (as used herein, unless otherwise specified, all number average molecular weights (M_n) refer to molecular weight measured in such manner). Thus, the polymeric material functions as a copolymeric compound. The copolymeric compound is polymerized from at least two monomeric components. Described herein are polymers wherein the first monomeric component is selected from one or more α,β-ethylenically unsaturated monomers containing at least one carboxylic acid group. This acid group can be derived from monoacids or diacids, anhydrides of dicarboxylic acids, monoesters of diacids, and salts thereof. The second monomeric component is
hydrophobically modified (relative to the first monomeric component) and is selected from one or more α,β-ethylenically unsaturated non-acid monomers containing a C_1 to C_9 alkyl group, including linear and branched C_1 to C_9 alkyl esters of (meth)acrylic acid, vinyl esters of linear and branched C_1 to C_{10} carboxylic acids, and mixtures thereof. In one aspect described herein, the second monomeric component is represented by the formula:

$$CH_2=CRX$$

wherein R is hydrogen or methyl; X is $-C(O)OR^1$ or $-OC(O)R^2$; R^1 is linear or branched C_1 to C_9 alkyl; and R^2 is hydrogen or linear or branched C_1 to C_9 alkyl. In another aspect of the invention R^1 and R^2 is linear or branched C_1 to C_8 alkyl and in a further aspect R^1 and R^2 are linear or branched C_2 to C_5 alkyl.

[0027] Thus, the hydrophobically modified polymers described herein comprise, consist essentially of and consist of a low molecular weight, non-crosslinked, linear acrylic copolymer derived from at least one first monomeric component selected from the group consisting of (meth)acrylic acid and at least one second monomeric component selected from the group consisting of one or more C_1 to C_9 alkyl (meth)acrylates, wherein the low molecular weight copolymer has a number average molecular weight of 100,000 or less.

[0028] Herein described first monomeric components include (meth)acrylic acid, itaconic acid, citraconic acid, maleic acid, fumaric acid, crotonic acid, aconitic acid, and mixtures thereof. Exemplary second monomeric components include ethyl (meth)acrylate, butyl (meth)acrylate, 2-ethylhexyl (meth)acrylate, vinyl formate, vinyl acetate, 1-methylvinyl acetate, vinyl propionate, vinyl butyrate, vinyl 2-ethylhexanoate, vinyl pivalate, vinyl neodecanoate, and mixtures thereof. As used herein, the terms "(meth)acrylic" acid and "(meth)acrylate" are meant to include the corresponding methyl derivatives of acrylic acid and the corresponding alkyl acrylate For example, "(meth)acrylic" acid refers to acrylic acid and/or methacrylic acid and "(meth)acrylate" refers to alkyl acrylate and/or alkyl methacrylate.

[0029] Also described herein are polymers wherein said first monomeric component is selected from the group consisting of (meth)acrylic acid and said second monomeric component is selected from the group consisting of at least one C_1 to C_9 alkyl (meth)acrylate.

[0030] The non-crosslinked, linear acrylic copolymer compounds used in the compositions of this invention can be synthesized via free radical polymerization techniques known in the art. In one aspect of the invention, the weight ratio of the first monomeric component to the second monomeric component utilized ranges from 20:80 to 50:50. In another aspect the weight ratio of the first monomeric component to the second monomeric component is 35:65, and in a further aspect the weight ratio of first monomeric component to second monomeric component is 25:75.

[0031] Methods of synthesizing the polymers useful in the compositions and methods of this invention may be found

in U.S. Patent No. 6,433,061.

[0032] The linear copolymeric materials useful in the methods and compositions of this invention preferably have a viscosity of 500 mPa·s or less (Brookfield RVT, 20 rpm, spindle no. 1) at a 5 wt. % polymer solids concentration in deionized water and neutralized to pH 7 with an 18 wt. % NaOH solution. The viscosity can range from 1 to 500 mPa·s in another aspect, from 10 to 250 mPa·s in a further aspect, and from 15 to 150 mPa·s in a still further aspect.

[0033] According to the invention, the low molecular weight, non-crosslinked linear acrylic copolymer present in the compositions of this invention is potassium acrylates copolymer.

[0034] The low molecular weight hydrophobically modified polymers used in the compositions of this invention are present in said compositions in amounts that are effective to inhibit, interfere with or degrade the collagen matrix in a wound healing model. Accordingly, the compositions of this invention degrade collagen and would therefore prevent the formation of keloid and hypertrophic scars. Preferably, they should be present in the compositions of this invention in an amount of from 0.1% to 100% percent by weight of the composition. More preferably, they should be present in the compositions of this invention in an amount of from 0.1% to 10% percent by weight of the composition. Even more preferably, they should be present in the amount of from 0.1% to 5% by weight of the composition. More preferably, they should be present in the amount of from 0.1% to 0.5% by weight of the composition. Most preferably, they should be present in the amount of from 0.1% to 0.5% by weight of the composition.

[0035] For injectible applications, the low MW HmP may be dissolved in phosphate buffered saline (abbreviated PBS). PBS is a buffer solution commonly used in biological research. It is a water-based salt solution containing sodium chloride, sodium phosphate, and, in some formulations, potassium chloride and potassium phosphate. The buffer's phosphate groups help to maintain a constant pH. The osmolarity and ion concentrations of the solution usually match those of the human body (isotonic). The preparation of a pharmacological composition that contains active ingredients dissolved or dispersed therein is well understood in the art and need not be limited based on formulation. Liquid preparations include solutions, suspensions, colloids, hydrogels, and emulsions, for example, water or water-propylene glycol mixtures. Such compositions may be prepared as injectables, either as liquid solutions or suspensions. Solid forms suitable for dissolving in a hydrogel or a liquid solution, or for suspending in liquid prior to use, can also be prepared. The preparation can also be emulsified. The active ingredient can be mixed with excipients which are pharmaceutically acceptable and compatible with the active ingredient and in amounts suitable for use in the therapeutic methods described herein. Suitable excipients include, for example, water, saline, dextrose, glycerol, ethanol or the like and combinations thereof. In addition, if desired, the composition can contain minor amounts of auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like which enhance the effectiveness of the active ingredient. Details on techniques for formulation and administration may be found in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing Co., Easton, Pa.).

[0036] The compositions of this invention may be in the form of a lotion or liquid capable of being applied on the surface of the skin or on an inanimate surface that has a wound. It may also be a composition which is applied directly to the skin or contained in an adhesive bandage (i.e., the treatment solution is contained with the absorbent portion of the bandage) and placed onto the skin surface having the wound. These types of composition may be more viscous and may be based on a gel or hydrogel composition.

[0037] The compositions of this invention may be made into a wide variety of product types that include but are not limited to liquids, lotions, creams, gels, sticks, sprays, shaving creams, ointments, cleansing liquid washes and solid bars, shampoos, pastes, powders, mousses, wipes, patches, wound dressing and adhesive bandages, hydrogels and films. These product types may contain several types of cosmetically acceptable topical carriers including, but not limited to solutions, emulsions (e.g., microemulsions and nanoemulsions), gels, solids and liposomes. The following are non-limiting examples of such carriers. Other carriers may be formulated by those skilled in the art of formulating such product types.

[0038] The topical compositions useful in this invention may be formulated as solutions. Solutions preferably contain an aqueous solvent (e.g., from 50% to 99.99% or from 90% to 99% of a cosmetically acceptable aqueous solvent).

[0039] Topical compositions useful in this invention may be formulated as a solution containing an emollient. Such compositions preferably contain from 2% to 50% of an emollient(s). As used herein, "emollients" refer to materials used for the prevention or relief of dryness, as well as for the protection of the skin. A wide variety of suitable emollients is known and may be used herein. Sagarin, Cosmetics, Science and Technology, 2nd Edition, Vol. 1, pp. 32-43 (1972) and the International Cosmetic Ingredient Dictionary and Handbook, eds. Wenninger and McEwen, pp. 1656-61, 1626, and 1654-55 (The Cosmetic, Toiletry, and Fragrance Assoc., Washington, D.C., 7th Edition, 1997) (hereinafter "ICI Handbook") contain numerous examples of materials for use in the compositions of this invention.

[0040] A lotion may also be made from such a solution. Lotions preferably contain from 1% to 20% (more preferably, from 5% to 10%) of an emollient(s) and from 50% to 90% (more preferably, from 60% to 80%) of water.

[0041] Another type of product that may be formulated from a solution is a cream. A cream preferably contains from 5% to 50% (more preferably, from 10% to 20%) of an emollient(s) and from 45% to 85% (more preferably from 50% to 75%) of water.

[0042] Yet another type of product that may be formulated from a solution is an ointment. An ointment may contain a simple base of animal or vegetable oils or semi-solid hydrocarbons. An ointment may preferably contain from 2% to 10% of an emollient(s) plus from 0.1% to 2% of a thickening agent(s). A more complete disclosure of thickening agents or viscosity increasing agents useful herein may be found in Sagarin, Cosmetics, Science and Technology, 2nd Edition, Vol. 1, pp. 72-73 (1972) and the ICI Handbook pp. 1693-1697.

[0043] The topical compositions useful in this invention may also be formulated as emulsions. If the carrier is an emulsion, preferably from 1% to 10% (e.g., from 2% to 5%) of the carrier contains an emulsifier(s). Emulsifiers may be nonionic, anionic or cationic. Suitable emulsifiers are set forth in, for example, U.S. Patent No. 3,755,560, U.S. Patent No. 4,421,769, McCutcheon's Detergents and Emulsifiers, North American Edition, pp. 317-324 (1986) and the ICI Handbook, pp.1673-1686.

[0044] Lotions and creams may also be formulated as emulsions. Preferably such lotions contain from 0.5% to 5% of an emulsifier(s). Such creams would preferably contain from 1% to 20% (more preferably, from 5% to 10%) of an emollient(s); from 20% to 80% (more preferably, from 30% to 70%) of water; and from 1% to 10% (more preferably, from 2% to 5%) of an emulsifier(s).

[0045] The compositions of this invention may be prepared in accordance with those methods and processes known to those of skill in the art, or in accordance with the methods of preparation of this invention. For example, water-soluble components such as glycerin, propylene glycol, sorbitol, inorganic base, preservatives, and the like may be dissolved in water and to that combination cellulose-derived polymers may be added. Another method of preparation is mixing all the ingredients into a slurry without water, and then adding the slurry to water.

[0046] The composition is preferably substantially free of surfactant, including anionic, cationic, amphoteric, or nonionic surfactants.

[0047] Included in a liquid or lotion formation of the composition may be water, oils, preservatives, emulsifiers, viscosity enhancers, emollients, electrolytes, fragrance, buffers, pH modifiers, skin protectants, metal ion sequestrants and the like.

Wound care bandage

[0048] Absorbent articles such as bandages may also be used to cover the open wound and deliver a treatment solution containing the low MW HmP. In this invention, any absorbent bandage may used. Typically, bandages have three layers: a skin facing layer, and absorbent layer and a top layer which faces away from the user's skin. The bottom layer of the bandage is oriented toward the user's skin and may be made of an aperture film or other material that does not stick to the wound but allows the treatment solution to penetrate. The absorbent layer may be made of absorbent fibers and contains the treatment solution. The top layer may also be an aperture film. The top layer may have a smaller open area than the bottom layer; this will prevent undesirable escape of the treatment solution from the absorbent layer. The bandages may be square, rectangular, round, oval or triangle in shape. The bandages may vary generally will range from 0.25 mm to 5 mm thick.

Materials

[0049] Potassium Acrylates copolymer (Lubrizol, Wickliffe, OH) was supplied as a 30% active formulation. The solution was diluted to 0.5% active and 5% active in distilled water, phosphate buffer saline (PBS), or acrylates cross-polymer-4 (SF2). The following solutions were supplied at different concentrations and all were diluted to 0.5% active formulation in water. EDP200 Ureido acrylic/methacrylic acid copolymer (Rhodia, Aubervillier, Cedex) was supplied at 17.7% active formulation. EDP 300 Ureido N, N-dimethylacrylamide methacrylic acid copolymer (Rhodia, Aubervillier, Cedex) was supplied at 16.4% active formulation. Polyacrylate-33 (Rhodia, Cranbury, NJ) was supplied at 29% active formulation. Acrylates Copolymer 4 (Lubrizol, Wickliffe, OH) was supplied at 32% active formulation. Acrylates Copolymer (Lubrizol, Pedricktown, NJ) was supplied at 30% active formulation. Inulin Lauryl Carbomate (Beneo-Bio Based Chemicals (Belgium) was supplied at 100% active formulation. Sodium Hydrolyzed Potato Starch Dodecenylsuccinate (Akzo Nobel, Salisbury, NC) was supplied at 100% active formulation. Octadecene/MA Copolymer (Chevron-Phillips, The Woodlands, Texas) was supplied at a 2% active formulation. Subdilutions were further made in water or phosphate buffered saline (PBS)(Mattek, Ashland, MA) for the experiments.

Example 1

Wound Healing Assay:

[0050] The wound healing experiment described below was used to evaluate the re-epithelialization properties of materials according to the invention. The experiment can also be used to determine collagen degradation of a formulation.

[0051] Full thickness skin equivalents were manufactured on a human collagen matrix plated with fibroblasts. Human

keratinocytes were cultured on top of the collagen matrix and then brought out of the medium to produce a differentiated stratum corneum. Full thickness equivalents were manufactured and ordered from Mattek (Ashland, MA), and the medium was ordered to include extra growth factors. The medium was also supplemented with 2% human serum (Lonza, Gampel, Valais). The equivalents were received and cultured following manufacturer instructions. A 3mm biopsy punch (Miltex, Plainsboro, NJ) was made in the middle of the skin tissue equivalent, removing the epidermal layer but leaving the collagen layer intact. 6 μL of the surfactant solution was applied to area of the biopsy punch. The equivalents were cultured according to manufacturer's instructions for five days. On the fifth day, the cells were harvested and transferred to a 10% formalin buffered solution (VWR, Bridgeport, NJ). The samples stained for Hematoxylin and eosin (H&E) staining (American Histolabs, Gaithersburg, MD). The samples were scanned at 4x using an Olympus BH2 microscope with movable stage (Center Valley, PA). They were then analyzed using the Nikon imaging software (NIS) (Melville, NY). Surface area and micron calculations were analyzed using the calibrated NIS software.

Table 1

Degradation of the collagen matrix measured by length of the collagen matrix in the middle of the wound bed.		
Material	INCI Name	Depth of the collagen matrix in the middle of the wound bed (μm)
0.5% active in PBS	Potassium Acrylates copolymer	77.26 ± 15.28*
0.5% active in Acrylates Crosspolymer-4	Potassium Acrylates copolymer	66.04 ± 14.79*
Vehicle control	Phosphate buffered saline	421.50 ± 22.85
Vehicle control	Acrylates Crosspolymer-4	414.94 ± 16.58
Numbers are reported ± SEM, *p<0.001 Compared by One Way ANOVA		

Results

[0052] 0.5% of active Potassium Acrylates copolymer caused significant degradation of the collagen matrix when tested in the wound healing model. Table 1 shows the depth of the collagen matrix measured in the middle of the wound bed. Potassium Acrylates copolymer was compared to another carbomer polymer, Acrylates Crosspolymer-4. Potassium Acrylates copolymer mixed with phosphate buffered saline (PBS) or Potassium Acrylates copolymer mixed with Acrylates Crosspolymer-4 caused significant degradation of the collagen matrix ($p<0.001$). Interestingly, only the collagen was degraded, the keratinocytes remained intact.

Example 2

Gelatin Degradation Assay

[0053] Gelatin is an irreversibly hydrolyzed form of collagen and is therefore a good model of collagen hydrogels. This experiment examines how compositions according to the invention containing different concentrations of potassium acrylates copolymer liquefy gelatin over time.

[0054] A 2.5% (w/v) purified gelatin (Amresco, Solon, OH)was made in phosphate buffered saline (Mattek, Ashland, MA) and heated to 80 °C until melted. The solution was cooled and placed into either 6 well or 24 well plates. The solution solidified at room temperature for a minimum of 24 hours. After the solid gel had formed, 100 μL of the various compositions containing potassium acrylates copolymer were added to solidified gelatin. At different time points, the samples were aspirated and weighed on an analytical balance to measure the amount of liquefied gelatin. The aspirated amounts were pipetted back into the wells after weighing. The experiments were ended after no longer than 6 days.

[0055] To confirm that Potassium Acrylates copolymer can degrade collagen, dilutions of Potassium Acrylates copolymer were applied to a purified gelatin matrix. 100 μL of Potassium Acrylates copolymer was applied in different concentrations to the gelatin hydrogels, the amount of liquefied gelatin was measured 48 hours after application, shown in Table 2.

Table 2. Potassium Acrylates Copolymer shows a dose dependent increase in liquefied gelatin 48 hours after application.

Material	Amount of liquefied gelatin (g)
Potassium Acrylates Copolymer 5% active in water	0.2457 ± 0.0175**
Potassium Acrylates Copolymer 0.5% active in water	0.1099 ± 0.0046**
Potassium Acrylates Copolymer 0.25% active in water	0.0629 ± 0.0030**
Potassium Acrylates Copolymer 0.1% active in water	0.0353 ± 0.0037*
Potassium Acrylates Copolymer 0.05% active in water	0.0244 ± 0.0028
Potassium Acrylates Copolymer 0.005% active in water	0.0142 ± 0.0025
Water	0.0190 ± 0.0021

Numbers are reported ± SEM, *p=0.05 compared to Water, **p<0.001 compared to water analyzed by One Way ANOVA.

[0056] Potassium Acrylates copolymer caused a dose dependent degradation of collagen at 48 hours after application; Potassium Acrylates copolymer at 0.1% active formulation caused significantly more degradation of the gelatin matrix than water. This continued the trend as the concentration of Potassium Acrylates copolymer increased in solution.

[0057] The ability for a HMP to degrade a collagen matrix is a specialized function that is not identical to all HMPs. This ability most likely has to do with the size and shape of the HMPs.

[0058] For example, Potassium Acrylates polymer, a mild, hydrophobically modified polymer surfactant shows a surprising ability to degrade collagen effectively at a wide range of concentrations. This has a wide range of clinical applications from reducing keloid scarring to reduction of collagen implants.

Claims

1. A composition comprising a potassium acrylates copolymer having a number average molecular weight of 100,000 or less as measured by gel permeation chromatography calibrated with a poly (methyl methacrylate) standard, for use in a method of improving the appearance of and/or substantially reducing the formation of scars and other visible effects of healed wounds, keloids and hypertrophic scars by degrading collagen, said method comprising contacting collagen contained within said scar tissue or wound with said composition in an amount effective to degrade said collagen.

2. A composition for use as claimed in claim 1, wherein said method comprises injectably applying said composition to a scar, healed wound, keloid or hypertrophic scar of a subject.

3. A composition for use as claimed in claim 1, wherein said method comprises topically applying said composition to a scar, healed wound, keloid or hypertrophic scar of a subject.

4. A composition for use as claimed in claim 1 wherein said composition further comprises a penetration enhancer.

5. A composition for use as claimed in claim 1 wherein said copolymer is present in said composition in an amount of from 0.1% to 10% percent by weight of the composition.

6. A composition for use as claimed in claim 1 wherein said composition further comprises at least 50% of protic solvent.

7. A composition for use as claimed in claim 1 wherein said composition comprises at least 97% of water.

8. A composition for use as claimed in claim 1 wherein said composition is applied using a mechanical penetration enhancer.

9. A composition for use as claimed in claim 1 wherein said composition comprises a dosage form selected from the group consisting of: a solution, a liquid, a lotion, a cream, a gel, a stick, a spray, a shaving cream, an ointment, a cleansing liquid wash, a solid bar, a shampoo, a paste, a powder, a mousse, a wipe, a patch, a wound dressing, an adhesive bandage, a hydrogel and a film.

Patentansprüche

1. Zusammensetzung, umfassend ein Kaliumacrylate-Copolymer mit einem zahlenmittleren Molekulargewicht von 100 000 oder weniger, wie anhand einer mit einem Polymethacrylsäuremethylester-Standard kalibrierten Gelpermeationschromatographie gemessen, zur Verwendung in einem Verfahren zur Verbesserung des Erscheinungsbildes von Narben und/oder wesentlicher Reduktion der Bildung von Narben und anderen sichtbaren Effekten von geheilten Wunden, Keloiden und hypertrophen Narben durch Abbau von Kollagen, wobei das Verfahren Kontaktieren von Kollagen, das in dem Narbengewebe oder der Wunde enthalten ist, mit der Zusammensetzung in einer effektiven Menge umfasst, um das Kollagen abzubauen.

2. Zusammensetzung zur Verwendung nach Anspruch 1, wobei das Verfahren das injizierbare Applizieren der Zusammensetzung auf eine Narbe, eine geheilte Wunde, ein Keloid oder eine hypertrophe Narbe eines Subjekts umfasst.

3. Zusammensetzung zur Verwendung nach Anspruch 1, wobei das Verfahren das topische Applizieren der Zusammensetzung auf eine Narbe, eine geheilte Wunde, ein Keloid oder eine hypertrophe Narbe eines Subjekts umfasst.

4. Zusammensetzung zur Verwendung nach Anspruch 1, wobei die Zusammensetzung ferner einen Penetrationsförderer umfasst.

5. Zusammensetzung zur Verwendung nach Anspruch 1, wobei das Copolymer in der Zusammensetzung in einer Menge von 0,1 Gew.% bis 10 Gew.% der Zusammensetzung vorhanden ist.

6. Zusammensetzung zur Verwendung nach Anspruch 1, wobei die Zusammensetzung ferner mindestens 50 % protisches Lösungsmittel umfasst.

7. Zusammensetzung zur Verwendung nach Anspruch 1, wobei die Zusammensetzung mindestens 97 % Wasser umfasst.

8. Zusammensetzung zur Verwendung nach Anspruch 1, wobei die Zusammensetzung unter Verwendung eines mechanischen Penetrationsförderers appliziert wird.

9. Zusammensetzung zur Verwendung nach Anspruch 1, wobei die Zusammensetzung eine Dosierform ausgewählt aus der Gruppe bestehend aus einer Lösung, einer Flüssigkeit, einer Lotion, einer Creme, einem Gel, einem Stift, einem Spray, einer Rasiercreme, einer Salbe, einem flüssigen Reinigungspräparat, einem festen Stück, einem Shampoo, einer Paste, einem Puder, einer Mousse, einem Wischtuch, einem Pflaster, einem Wundverband, einem Heftpflaster, einem Hydrogel und einem Film umfasst.

Revendications

1. Composition comprenant un copolymère d'acrylates de potassium présentant une moyenne en nombre du poids moléculaire de 100 000 ou moins telle que mesurée par chromatographie sur gel étalonnée avec un étalon de poly(méthacrylate de méthyle), pour une utilisation dans une méthode destinée à améliorer l'aspect et/ou sensiblement réduire la formation de cicatrices et d'autres effets visibles de plaies guéries, de kéloïdes et de cicatrices hypertrophiques par dégradation de collagène, ladite méthode comprenant la mise en contact de collagène contenu au sein dudit tissu ou de ladite plaie cicatriciel(le) avec ladite composition selon une quantité efficace pour dégrader ledit collagène.

2. Composition pour une utilisation selon la revendication 1, où ladite méthode comprend l'application par voie injectable de ladite composition à une cicatrice, une plaie guérie, un kéloïde ou une cicatrice hypertrophique, d'un sujet.

3. Composition pour une utilisation selon la revendication 1, où ladite méthode comprend l'application par voie topique de ladite composition à une cicatrice, une plaie guérie, un kéloïde ou une cicatrice hypertrophique, d'un sujet.

4. Composition pour une utilisation selon la revendication 1, où ladite composition comprend en outre un améliorateur de pénétration.

5. Composition pour une utilisation selon la revendication 1, où ledit copolymère est présent dans ladite composition selon une quantité allant de 0,1% à 10% en poids de la composition.

6. Composition pour une utilisation selon la revendication 1, où ladite composition comprend en outre au moins 50% d'un solvant protique.

7. Composition pour une utilisation selon la revendication 1, où ladite composition comprend au moins 97% d'eau.

8. Composition pour une utilisation selon la revendication 1, où ladite composition est appliquée à l'aide d'un améliorateur de pénétration mécanique.

9. Composition pour une utilisation selon la revendication 1, où ladite composition comprend une forme de dosage choisie dans le groupe constitué par : une solution, un liquide, une lotion, une crème, un gel, un bâtonnet, un spray, une crème de rasage, un onguent, une lotion de nettoyage liquide, un pain solide, un shampooing, une pâte, une poudre, une mousse, une lingette, un patch, un pansement pour plaies, un bandage adhésif, un hydrogel et un film.

REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

- WO 2005105115 A1 **[0008]**
- US 7879823 B **[0022]**
- US 7179475 B **[0022]**
- US 6890553 B **[0022]**
- US 20120321574 A **[0022]**
- US 6433061 B, Marchant **[0026] [0031]**
- US 3755560 A **[0043]**
- US 4421769 A **[0043]**

Non-patent literature cited in the description

- Remington's Pharmaceutical Sciences. Maack Publishing Co, **[0020] [0035]**
- **SAGARIN.** Cosmetics, Science and Technology. 1972, vol. 1, 32-43 **[0039]**
- the International Cosmetic Ingredient Dictionary and Handbook. The Cosmetic, Toiletry, and Fragrance Assoc, 1997, 1656-61 **[0039]**
- **SAGARIN.** Cosmetics, Science and Technology. 1972, vol. 1, 72-73 **[0042]**
- the ICI Handbook. 1693-1697 **[0042]**
- McCutcheon's Detergents and Emulsifiers. 1986, 317-324 **[0043]**
- the ICI Handbook. 1673-1686 **[0043]**